REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-53 are in this case. Claims 9-53 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-8 have been rejected. Claim 1 has now been amended.

The claims before the Examiner are directed at a biological preparation for in vivo use which includes a biological material, such as, cells, tissue or a drug delivery system (e.g., liposomes or granules) to which extracellular matrix degrading enzyme is externally adhered, so as to enhance extravasation of the biological material *in vivo*.

Specification

The Examiner has objected the disclosure for certain informalities which have now been corrected.

35 U.S.C. § 102(b) Rejections - Fuks et al.

The Examiner has rejected claims 1 and 6 under 35 U.S.C. § 102(b) as being anticipated by Fuks et al. The Examiner's rejections are respectfully traversed. Claim 1 has now been amended.

The Examiner points out that Fuks et al. teach substantially purified heparanase and the use thereof as a basis for a pharmaceutical composition which includes the heparanase and a pharmaceutically acceptable carrier, such as a slow release carrier, useful in the process of wound healing. The Examiner further points out that pharmaceutically acceptable slow releasing carriers encompass drug delivery systems such as liposomes, granules and the like, as defined in the instant application.

Claim 1 of the instant application is directed at the combination of a biological material and a purified, natural or recombinant, extracellular matrix degrading enzyme, which is externally adhered thereto.

Pharmaceutically acceptable slow releasing carriers which indeed encompass drug delivery systems such as liposomes, granules and the like, as is defined in the instant application, are known to include their pharmaceutically active ingredients within their volume as opposed to externally thereto.

In sharp distinction, claim 1 recites that the extracellular matrix degrading enzyme is externally adhered to the biological material (e.g., a drug delivery system).

A drug delivery system is defined in the specification of the instant application to include:

> ... liposomes, granules and the like which include an inner volume containing a drug which is thereafter released therefrom.

Thus, independent claim 1 and claim 6 which directly depends therefrom read on a drug delivery system which on one hand contains therein a drug which has a therapeutic effect and on the other hand is externally coated with an extracellular matrix degrading enzyme which facilitates the propagation of the drug delivery system through extracellular matrix.

While continuing to traverse the Examiner's rejections, Applicant has chosen, in order to expedite prosecution, to amend independent claim 1, so as to further distinct the present invention as claimed in independent claim 1 from the Fuks et al. patent.

In particular, claim 1 has now been amended to recite that the extracellular matrix degrading enzyme which is externally adhered to the biological material serves to enhance extravasation of the biological material *in vivo*.

Support for the above amendment is found is the specification. To this end, see, for example, page 4, lines 18-20, reciting in this respect that:

> Cleavage of heparan sulfate by heparanase may therefore result in disassembly of the subendothelial ECM and hence may play a decisive role in extravasation of normal and malignant blood-borne cells

page 16, lines 18-20, reciting that:

> It has been, therefore, proposed that the cytotrophoblastic heparanase facilitates placentation, through cytotrophoblast extravasation and localized neovascularization

and by the Experimental Results which show that (i) heparanase which is externally adhered to cells retains its catalytic activity and is also activated if adhered in an inactive form; and (ii) that cancer cells to which catalitycally active heparanase is externally adhered are characterized by enhanced extravasation, as is evident by their higher metastatic performance, as is compared to control cells to which no heparanase or other extracellular degrading enzyme has been externally adhered.

Thus, while Fuks et al. teach the use of heparanase as a pharmaceutically active ingredient occluded within drug delivery systems such as liposomes and granules to facilitate wound healing while being slow released therefrom, the present invention as claimed in independent claim 1 teaches the use of an extracellular matrix degrading enzyme, such as heparanase, which is externally adhered to a biological material, such as a drug delivery system, to enhance extravasation in vivo. In other words, both structural and functional differences exist between the present invention as claimed and the teachings of Fuks et al.

It is therefore the Applicant's strong opinion that the present invention as claimed is not anticipated, nor is it rendered obvious by the teachings of Fuks et al.

It is therefore the Applicant's opinion that claims 1 and 6 are allowable.

35 U.S.C. § 102(b) Rejections - Sigma Catalog

The Examiner has rejected claims 1, 2, 4 and 7 under 35 U.S.C. § 102(b) as being anticipated by the Sigma Catalog. The Examiner's rejections are respectfully traversed. Claim 1 has now been amended.

The Examiner points out that Sigma sells and teaches the use of collagenase for the hydrolysis of native collagen in the isolation of cells from animal tissue and tissue culture. The Examiner concludes that Sigma teaches a biological preparation comprising a biological material and the extracellular matrix degrading enzyme, collagenase, wherein the biological material is a plurality of cells or tissue to be dissociated and as such anticipates the claims 1, 2, 4 and 7.

The Examiner's attention is respectfully drawn to the fact that the use of collagenase as taught by Sigma is for dissociating cells in a biological sample, which is clearly not the case of the present invention as claimed in independent claim 1. In claim 1, the extracellular matrix degrading enzyme is said to be externally adhered to a biological material (e.g., cells or tissues). Being adhered thereto, the enzyme is used to assist such biological material in extravasation in vivo. In sharp contrast, the enzyme as taught by Sigma, is used for dissociating a biological sample into individual cells.

A biological preparation as taught by Sigma is not applicable for use in vivo because, either the cells are mixed with debris, or the individual cells are washed several times so as to remove the collagenase therefrom, or the cells are replated, i.e., diluted to such a fold and in a solution such that they are no longer applicable for in vivo use.

While continuing to traverse the Examiner's rejections, Applicant has chosen, in order to expedite prosecution, to amend independent claim 1, so as to further distinct the present invention as claimed from the teachings of the sigma Catalog. In particular, claim 1 has now been amended to recite that the cell preparation is for in vivo use and that the extracellular matrix degrading enzyme which is externally adhered to the biological material serves to enhance extravasation of the biological material *in vivo*.

Furthermore, collagenase is taught by Sigma as a replacement for trypsin treatment (as taught, for example, by the Examples section of the instant application) for cell dissociation. Following collagenization or trypsinization cells are thoroughly washed so as to remove residual enzyme activity.

It is therefore the Applicant's strong opinion that the present invention as claimed is not anticipated, nor is it rendered obvious, by the teachings of The Sigma Catalog.

It is therefore the Applicant's opinion that claims 1, 2, 4 and 7 are allowable.

35 U.S.C. § 103(a) Rejections - Fuks et al. and Wang et al.

The Examiner has rejected claims 1-5, 7 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Fuks et al. and Wang et al. The Examiner's rejections are respectfully traversed. Claim 1 has now been amended.

The Examiner points out that both Fuks et al. and Wang et al. teach that heparanase, while degrading extracellular matrix in vivo, releases therefrom factors which can assist in various healing processes and even name some of them. This function of heparanase is well known to the Applicants as is evident from the background section of the instant application.

However, the present invention as claimed uses the extracellular matrix degrading activity of heparanase or other extracellular matrix degrading enzymes so as to assist extravasation of a biological material within the body not through a secondary effect of releasing factors from the extracellular matrix, rather by the direct effect of degrading the extracellular matrix.

As discussed above, Fuks et al., and for that matter also Wang et al., both fail to teach or suggest a biological material to which heparanase, or for that matter any other extracellular matrix degrading enzyme, is externally adhered.

Thus, since both the structural elements and the mode of functioning of the present invention as claimed differ from the teachings of the Fuks et al. and/or Wang et al., it is argued that the Sigma Catalog fails to render the present invention as claimed obvious.

It is therefore the Applicant's opinion that claims 1-5, 7 and 8 are allowable.

35 U.S.C. § 103(a) Rejections - Sigma Catalog

The Examiner has rejected claims 3 and 5 under 35 U.S.C. § 103(a) as being unpatentable over the Sigma Catalog. The Examiner's rejections are respectfully traversed.

The Examiner points out that Sigma sells and teaches the use of collagenase of various forms for the hydrolysis of native collagen in the isolation of cells from animal tissue and tissue culture. The examiner further points out that any type of cell may be subject to collagenase treatment as taught by Sigma in conjunction with a limited list of cell types. The Examiner concludes that Sigma teaches a biological preparation comprising cells in culture or a tissue of any type and the extracellular matrix degrading enzyme, collagenase, wherein the cells are to be dissociated from the culture or tissue and as such renders claims 3 and 5 obvious.

The Examiner's attention is respectfully drawn again to the fact that the use of collagenase as taught by Sigma is for dissociating cells in a biological sample, which is clearly not the case of the present invention as claimed. In claim 1, from which claims 3 and 5 depend, the extracellular matrix degrading enzyme is said to be externally adhered to a biological material (e.g., cells or tissues). Being adhered thereto, the enzyme is used to assist such biological material in extravasation in vivo. In sharp contrast, the enzyme as taught by Sigma, is used for dissociating a biological sample into individual cells.

A biological preparation as taught by Sigma is not applicable for use in vivo because, either the cells are mixed with debris, or the individual cells are washed several times so as to remove the collagenase therefrom, or the cells are replated, i.e., diluted to such a fold and in a solution such that they are no longer applicable for in vivo use.

While continuing to traverse the Examiner's rejections, Applicant has chosen, in order to expedite prosecution, to amend independent claim 1, from which claims 3 and 5 depend, so as to further distinct the present invention as claimed from the teachings of the sigma Catalog. In particular, claim 1 has now been amended to recite that the cell preparation is for in vivo use and that the extracellular matrix degrading enzyme which is externally adhered to the biological material serves to enhance extravasation of the biological material *in vivo*.

It is therefore the Applicant's strong opinion that the present invention as claimed is not anticipated, nor is it rendered obvious by the teachings of The Sigma Catalog.

It is therefore the Applicant's opinion that claims 3 and 5 are allowable.

In view of the above amendments and remarks it is respectfully submitted that claims 1-8 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Enc.:
1. Late Response Fee